NO:4, wherein the antibody binds to the same epitope as an RFB4 antibody comprising a V_H chain of SEQ ID NO:2 and a V_L chain of SEQ ID NO:4.

45. (new) The anti-CD22 antibody of claim 44, wherein said antibody is detectably labeled.

46. (new) The antibody of claim 44, wherein said antibody is conjugated to a therapeutic agent.

C7

47. (new) The antibody of claim 46, wherein said therapeutic agent is a *Pseudomonas* exotoxin (PE) or cytotoxic fragment thereof.

48. (new) A method for detecting the presence of CD22 protein in a biological sample, said method comprising:

(a) contacting said biological sample with an anti-CD22 antibody of claim 44;

(b) binding said antibody to said CD22 protein under immunologically reactive conditions to form an antibody-CD22 protein complex, wherein detection of said complex indicates the presence of said CD22 protein.

49. (new) The method of claim 48, wherein said antibody is detectably labeled.

REMARKS

With entry of the present amendment claims 1-7, claims 18-21 and 32-39 have been canceled, new claims 40-49 have been added, and claims 1, 5-8, 11, 12,15, 22, and 27-30 have been amended. These amendments add no new matter and are supported throughout the specification, claims, and drawings as filed.

The amendment to the specification substitutes a revised sequence listing that corrects the inadvertent error in the previous sequence listing submitted on May 11, 2000. The amendment adds no new matter and is supported by the application as filed.

Claims 1 and 11 have been amended to recite an antibody that binds an extracellular epitope of CD22. Support for the amendment can be found throughout the specification, claims, and drawings as originally filed, *e.g.*, page 20, lines 31-32.

Claims 5, 12, and 27 have been amended to recite a binding fragment that binds to the same epitope as an RFB4 disulfide-stabilized F_V. Support for the amendment can be found throughout the specification, claims, and drawings as originally filed, *e.g.*, page 15, lines 10-11.

Claims 5, 12, and 27 have been amended to recite an RFB4 disulfide-stabilized Fv comprising a variable heavy chain as set out in SEQ ID NO:2, wherein a Cys residue is substituted for Arg at position 44; and a variable light chain as set out in SEQ ID NO:4, wherein a Cys residue is substituted for Gly at position 100. Support for the amendment can be found throughout the specification, claims, and drawings as originally filed, *e.g.*, Figure 1 and page 39, lines 14-33.

Claims 6, 15, and 28 have been amended to recite a variable heavy chain and a variable light chain at least 90% identical to SEQ ID NO:2 and SEQ ID NO:4, respectively, over a comparison window of 10 amino acids. Support for the amendment can be found throughout the specification, claims, and drawings as originally filed, *e.g.*, page 12, lines 19-22.

New claims 40 and 41 recite an isolated nucleic acid encoding a V_H chain (claim 40) or a V_L chain (claim 41) comprising an amino acid sequence as set out in SEQ ID NO:2 or SEQ ID NO:4, respectively. Support for the amendment can be found throughout the specification, claims, and drawings as originally filed, *e.g.*, page 12, lines 19-22.

New claims 42 and 43 recite an isolated nucleic acid encoding a V_H chain (claim 42) or a V_L chain (claim 43) comprising a conservatively modified variant of an amino acid sequence set forth in SEQ ID NO:2 and SEQ ID NO:4, respectively. Support for the amendment can be found throughout the specification, claims, and drawings as originally filed, *e.g.*, page 12, lines 1-11.

New claim 44 recites an antibody that binds to an extracellular epitope of CD22 comprising a variable heavy chain that is a conservatively modified variant of SEQ ID NO:2 and a variable light chain that is a conservatively modified variant of SEQ ID NO:4. Support for the amendment can be found throughout the specification, claims, and drawings as originally filed, *e.g.*, page 12, lines 1-9.

For convenience, the Examiner's rejections are addressed in the order in which they were presented in the November 2, 2000 Office Action.

1. The invention

The invention relates to recombinant immunoconjugates that are highly specific for CD22, nucleic acids encoding such immunoconjugates, and methods of using the immunoconjugates

to detect or to inhibit the growth of a malignant B-cell. The immunoconjugates comprises a therapeutic agent or detectable label that is covalently linked to a recombinant anti-CD22 antibody that is stabilized by a disulfide linkage. The CD22 antibody comprises a variable heavy chain with a cysteine at amino acid position 44 and a variable light chain with a cysteine at amino acid position 100. Such immunoconjugates exhibit increased stability and potency.

2. Objections to the claims

Claim 37 was objected to because the claim as-filed recites a V_L of SEQ ID NO:2. The objection is obviated by the cancellation of claim 37.

3. Rejections under 35 U.S.C. § 112, second paragraph.

The Examiner has rejected claims 1-10, 12, 15, 16, and 18-39 as allegedly indefinite. Each of the individual rejections are discussed below, in the order presented by the Examiner.

Claims 1, 7, 8, 29, and 30 were rejected as allegedly indefinite for reciting "bonded" because the exact meaning of the term is not clear. Applicants respectfully disagree and note that the claim refers to "peptide bonded", which is well known in the art. However, in order to expedite prosecution, the claims have been amended to replace "peptide bonded" with "covalently linked". Applicants note that peptide bonds are one form of covalent linkage and that the amendment therefore does not exclude peptide bonds. Applicants therefore respectfully request withdrawal of the rejection.

Claims 5, 12, and 27 were rejected as allegedly indefinite for reciting the term "RFB4" because other laboratories or inventors may use the same laboratory designation for different antibodies. Applicants respectfully disagree with the Examiner. RFB4 is defined in the specification as referring to an anti-CD22 antibody, moreover, the antibody is commercially available under the name "RFB4". Applicants therefore maintain that the designation is clear. However, in order to expedite prosecution, the claims have been amended to refer to SEQ ID NOs. Applicants therefore respectfully request withdrawal of the rejection.

Claims 6, 15, 18-21, 33, and 37 were rejected as allegedly indefinite for reciting the phrase "substantially similar". The rejection is obviated with regard to claims 33 and 37 in view of their cancellation. To the extent that the rejection applies to the amended claims, Applicants traverse. As noted by the Examiner, the specification provides a definition of the term at page 12 in

the specification. This definition refers to sequence identity, which is commonly used in the genetic analysis art (*see, e.g.,* the Examiner's comments regarding a reference, Rodriguez *et al*, which is described as teaching an amino acid sequence "that is 97% identical to SEQ ID NO:4") and is further defined on pages 12 and 13. Moreover, a definition of "comparison window" is included on page 13. Accordingly, "substantially similar" is fully defined when read in light of the specification. However, in order to expedite prosecution, the claims have been amended to recite "90% sequence identity over a window of 10 amino acids". Applicants therefore request withdrawal of the rejection.

Claim 12 was rejected as allegedly indefinite because of the abbreviation "dsFv". The claim has been amended to recite "disulfide-stabilized Fv (dsFv)". Applicants therefore request withdrawal of the rejection.

Claims 22-32 were rejected as allegedly indefinite for reciting incomplete method claims that do not clearly set forth method steps or a resolution step that reads back on the preamble of the claimed method. Although Applicants maintain that the claims as filed provide positive steps to perform the method, in order to expedite prosecution, claim 22 has been amended to refer back to the preamble. Applicants therefore respectfully request withdrawal of the rejection.

Claim 34 was rejected as allegedly indefinite for insufficient antecedent basis. This rejection is obviated in view of the cancellation of the claim.

Claims 5 and 27 were rejected as allegedly indefinite in the recitation of "RFB4 binding fragment". Although Applicants disagree with the rejection because "RFB4 binding fragment" is defined on page 15 of the specification, in order to expedite prosecution, the claims have been amended to recite language included in the definition. Applicants therefore request withdrawal of the rejection.

Claims 1-17 and 22-32 were rejected as allegedly indefinite for reciting amino acid positions "44" and "100" in claims 1 and 11. Applicants respectfully traverse the rejection. The specification unambiguously indicates that the amino acid positions of V_H or V_L are determined with reference to Kabat and Wu, which citation is provided in the specification and is incorporated by reference. (*see, e.g.*, the specification at page 19, last paragraph, bridging to page 20). The MPEP at § 2173.05 indicates that the meaning of every term used in a claim should be apparent from the prior art *or from the specification and drawings at the time the application is filed* (emphasis added). Applicants submit that the claims meet this requirement and therefore respectfully request withdrawal of the rejection.

4. Rejections under 35 U.S.C. § 112, first paragraph.

The sequence listing submitted herewith is supported by the application as-filed.

Claims 6, 8-10, 15-21, 28, and 33-39 were rejected as allegedly containing subject matter that was not described in the specification in such a way as to convey that the inventor, at the time the application was filed, had possession of the claimed invention. The rejection alleges that SEQ ID NOs:1-4 as disclosed in the amendment submitted on May 11, 2000 were not disclosed in Figure 1 of the application as filed. The rejection is traversed in part and obviated in part by the submission of a corrected sequence listing.

SEQ ID NO:1, a nucleic acid encoding the heavy chain of RFB4, shows a GTC codon at the position corresponding to amino acid position 121. The GTC codon is set out in Figure 1, but is incorrectly identified as encoding a Thr residue. The specification at page 39, lines 1-4 indicates that the amino acid sequence was deduced from the nucleic acid sequence. Accordingly, the nucleic acid sequence as provided indicates the sequence of the heavy chain. Thus, the valine residue set out in SEQ ID NO:2, the amino acid sequence of the heavy chain, is fully supported by the specification. Accordingly, the sequence listing submitted herewith includes the nucleic acid sequence of Figure 1 as SEQ ID NO:1 and the amino acid sequence deduced from the nucleic acid sequence of Figure 1 as SEQ ID NO:2.

SEQ ID NO:3 in the revised sequence listing submitted herewith corrects a typographical error in the previously filed sequence listing, in which the codon encoding the residue at position 61 of the RFB4 light chain was inadvertently shown as AAG, which encodes Lys. The codon has been corrected to read AGG, which encodes an Arg residue. The AGG codon is shown in Figure 1 of the application as filed, and is identified as encoding Arg.

In view of these remarks and the submission of a corrected sequence listing, Applicants respectfully request withdrawal of the rejection.

Guidance to make and use the immunoconjugates of the invention is provided.

Claims 1-5, 7-14, 17-19, 22-24, 26-27, 29-32, and 39 are rejected as allegedly not enabled. Applicants traverse the rejection.

Applicants first thank the Examiner for acknowledging that the specification is enabled for an immunoconjugate comprising a PE toxin or PE38 toxin or a detectable label linked to

a recombinant anti-CD22 antibody of RFB4 with a V_L of SEQ ID NO:4 which contains a cysteine at amino acid position 100, and a V_H of SEQ ID NO:2 with a cysteine at position 44. The Examiner further acknowledges that the specification is enabling, relative to such an immunoconjugate, for a V_H chain that is covalently attached the amino terminus of PE or PE38; the V_L and V_H linked through a linker peptide or through a cysteine-cysteine disulfide bond; an expression cassette encoding the immunoconjugate and a host cell; and a method of inhibiting the growth of a rodent, canine, or primate malignant B cell.

The rejection appears to allege that the specification is not enabling for an immunoconjugate comprising any recombinant anti-CD22 antibody because the claims read on antibodies that do not bind antigen. The rejection also alleges that the V_H of SEQ ID NO:2 or V_L of SEQ ID NO:4 would separately not bind antigen. Lastly, the rejection appears to allege that the specification is not enabled for a method of inhibiting the growth of any malignant B-cell with a conjugate with a detectable label, or a method of inhibiting the growth of malignant B cells *in vivo* in humans, or detecting the presence of CD22 *in vivo* in a mammal including a human. Applicants disagree.

As discussed in the rejection, in determining whether undue experimentation is required to practice the claimed invention, factors such as the amount of guidance presented in the specification and the presence of working examples must be considered (*see*, *Ex Parte Forman*, 230 USPQ 546 (Bd. Patent App. & Int. 1985)). In *In re Wands*, 8 USPQ2d 1400 (Fed. Circ 1988) the Federal Circuit noted, "a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed" (*see*, *Wands*, 8 USPQ2d at 1404, quoting *In re Jackson*, 217 USPQ 804 (Bd. Pat. App. & Int. 1982). Thus, Applicants are not required to disclose every conceivable anti-CD22 for the disclosure to be enabling, but must provide sufficient guidance.

Applicants submit that ample guidance is provided in the specification to make and use the claimed immunoconjugates. For example, at pages 16 through 21, Applicants have described assays to identify antibodies that selectively bind to CD22, and methods of producing such antibodies. At pages 19-20, the specification teaches the identification of position 44 of a V_H and position 100 of a V_L such that cysteine residues can be incorporated as defined by the claims. As known to those of skill in the art, (*see*, *e.g.*, Reiter *et al.*, *Biochemistry* 33:5451-5459, 1994), these

locations for cysteine substitution can be readily identified by aligning the sequences due to the highly conserved nature of the framework residues (Reiter *et al.*, *supra*, page 5457, second column, first paragraph). The specification also teaches the production of recombinant immunoconjugates (*see, e.g.*, the section starting at page 23) and administration of pharmaceutical compositions (*see, e.g.*, the section starting at page 27). Moreover, Applicants have provided Examples to illustrate each of these aspects of the invention and have provided information for the skilled artisan to identify preferred embodiments of anti-CD22 antibodies. Thus, the specification provides the requisite guidance with respect to the direction in which the experimentation should proceed and accordingly, enables the claimed invention.

The rejection also appears assert that the claims are not enabled because they read on an anti-CD22 antibody that does not have to bind antigen. Applicants note that use of the term "anti-CD22 antibody" in the claims accords with the definition of anti-CD22 antibody provided in the specification, *e.g.*, at page 16, which states that the antibodies of the present invention "are selectively reactive under immunological conditions to those determinants of CD22 displayed on the surface of B-cells and accessible to the antibody from the extracellular milieu." The specification further defines "selectively reactive" in terms of specific binding to CD22. Accordingly, an anti-CD22 antibody, as used in the claims, binds CD22. However, in order to expedite prosecution, the claims have been amended to include additional language that emphasizes that the claims are directed to antibodies that bind CD22. Applicants therefore respectfully request withdrawal of the rejection.

The claims enable use of the claimed immunoconjugates *in vivo* in a human.

The rejection also alleges that the specification does not enable an immunoconjugate that would inhibit the growth of malignant B-cells *in vivo* in a human. Applicants traverse the rejection.

As acknowledged by the Examiner, Applicants have provided evidence that the claimed immunoconjugates inhibit the growth of malignant human B-cells that express CD22 *in vivo*. In these experiments, the immunoconjugates were administered to athymic mice with established human tumors (*see, e.g.*, Example 8). The results show that administration of the RFB4(dsFV) immunoconjugate inhibited growth of the tumor cells.

The rejection points to a publication by Chatterjee *et al.* as allegedly supporting the assertion that the results in a mouse animal model often differ from the clinical response obtained in patients. Applicants note that the cited art appears to focus on work that involved animal tumors as a model for human tumors (*see, e.g.*, the Introduction, page 75, which states that "These clinical trials are based on a large body of experiments in animal models in which significant immunological evidence and therapeutic results in *animal tumors* have been obtained", emphasis added). Further, Ghetie *et al.* appear to support the use of an *in vivo* model of a mouse bearing human tumor cells as an accepted model for correlation with use in a human (*see, e.g.*, page 5879, column 1, which states that "In order to optimize strategies for using ITs in humans, it is advantageous to have a murine model of disseminated human B cell lymphoma in mice."). Furthermore, as discussed above, the specification teaches administration of pharmaceutical compositions to humans (*see, e.g.*, the section starting at page 27). Accordingly, based on the disclosure in the application coupled with information known in the art, Applicants have taught one skilled in the art to make or use the claimed invention without undue experimentation.

To further demonstrate that the disclosure is enabling for *in vivo* use in humans, a Declaration by David J. Fitzgerald is submitted herewith. The Declaration provides evidence that a compound made and used *in vivo* in humans in accordance with the teachings in the specification inhibits the growth of B cells that express CD22.

The Declaration describes the use of an immunoconjugate RFB4(dsFv)-PE38, referred to as BL22, which is a recombinant immunotoxin comprising an anti-CD22 disulfide-stabilized Fv fused to a truncated *Pseudomonas* exotoxin. The immunotoxin comprises an anti-CD22 antibody having a V_H with a cysteine residue at position 44 and a V_L with a cysteine amino acid position 100. Toxicity and activity of the immunoconjugate was assessed in patients with purine-resistant hairy cell leukemia in a dose-escalation trial. The results demonstrated a high response rate: of the 16 purine analog-resistant hairy cell leukemia patients, 11 achieved complete remissions and 2 achieved partial responses. All 3 of the non responders received low doses of BL22 or had preexisting antitoxin antibodies.

The immunoconjugate was administered to 16 patients with hairy cell leukemia, a B-cell malignancy, in a dose-escalation trial by 30 minutes intravenous infusion every other day for 3 doses. All patients had $CD22^+$ malignant cells by either flow cytometry or immuno-histochemistry. Further, the malignant disease in each of the 16 patients was resistant to standard chemotherapy. BL22 was

diluted into 50 mL of 0.2 percent albumin in 0.9 percent sodium chloride and administered as a 30 minute intravenous infusion every other day for 3 doses. The cycles and doses are provided in Table I of Exhibit 2 provided with the Declaration. Disease was assessed by whole body computed tomography (CT), flow cytometry and PCR of blood, and histopathology of bone marrow. Determination of BL22 plasma levels and neutralizing antibodies was by cytotoxicity assay on Raji cells. All responders had rapid reduction in circulating hairy cell leukemia cells, which indicates a direct cytotoxic effect of BL22. Thus, administration of BL22 results in inhibition of growth of malignant B-cells that express $CD22^+$ on the surface.

Therefore, in view of the enabling disclosure, and the amount of guidance provided to those of skill in the art, no undue experimentation is required to make and use the immunoconjugates of the invention *in vivo* in a human. Accordingly, Applicants respectfully request withdrawal of the rejection.

The rejection also alleges that the disclosure does not enable detection of CD22 *in vivo* in a human (applied to claim 39). Applicants submit that the rejection is obviated by the cancellation of claim 39.

The claims have been amended to recite the SEQ ID NOs referring to the variable region sequence for RFB4.

Claims 5, 12, and 27 were rejected as allegedly not enabled in the recitation of the antibody RFB4. The claims have been amended to recite the SEQ ID NOs referring to the variable region sequence for RFB4. Therefore, one of skill in the art can, without undue experimentation, reproduce the RFB4 antibody. Applicants therefore respectfully request withdrawal of the rejection.

5. Priority

The Office Action alleges that the limitation of the SEQ ID NOs. are not found in the provisional application filed 3/20/97 and concludes that claims 6, 8-10, 15, 21, 28, and 33-39 have a filing date of the present application, which was alleged to be February 17, 2000. Applicants note that the sequence listing has been corrected to reflect the nucleic acid sequences (and the amino acid encoded by the nucleic acid sequences) provided in Figure 1. As discussed above, these sequences are fully supported by the specification of the provisional application 60/041,437 filed March 20, 1997.

Applicants further note that the present application was filed under 35 U.S.C. 371 and that the filing date of the present application is the filing date of the international application (*see, e.g.*, MPEP 1893.03(b)) of March 19, 1998, as noted on the Notification of Acceptance of Application Under 35 U.S.C. 371 for the present application.

6. Rejections under 35 U.S.C. § 102.

The rejection alleges that claims 6, 8-10, 15-21, 28, and 33-39 as allegedly anticipated by Fitzgerald *et al.* (WO 98/41641). Applicants traverse the rejection. The present application is a 35 U.S.C. 371 application of PCT/US98/05453, which published as WO 98/41641 and the true filing date of the present application is the filing date of the international application (*see, e.g.*, MPEP 1893.03(b)). The rejection is therefore moot and Applicants respectfully request withdrawal.

Claim 19 was rejected as allegedly anticipated by Rodriguez *et al.* In view of the cancellation of claim 19, Applicants respectfully request withdrawal of the rejection.

Claims 6, 8, 10, 18, 19, 28, 33, and 35-37 were rejected as allegedly anticipated by Kreitman *et al* (*Proc. of the American Association for Cancer Res.* 38:28, 1997). Applicants submit that the rejection is obviated by submission of a revised sequence listing fully supported by the priority application. Applicants therefore respectfully request withdrawal of the rejection.

Claims 33 and 35 were rejected as allegedly anticipated by Ghetie *et al.* The rejection alleges that Ghetie *et al.* have produced an antibody that is identical to the claimed antibody RFB4 which has the same VH and VL as claimed and can be used to assay the same CD22 protein. The rejection is obviated by the cancellation of claims 33 and 35. Applicants therefore respectfully request withdrawal of the rejection.

7. Rejections under 35 U.S.C. § 103

Claims 1-32 were rejected as allegedly unpatentable over Ghetie *et al.* and further in view of Reiter *et al.* and Kuan *et al.* The rejection alleges that it would have been *prima facie* obvious to have used the antibody RFB4 and method of inhibiting malignant B cells as taught by Ghetie *et al.*, and the method of Reiter *et al.* and Kuan e*t al.* to produce a disulfide-stabilized anti-CD22 antibody conjugate. The rejection further alleges that one of ordinary skill would have been motivated to do so, and had a reasonable expectation of success, because Ghetie *et al.* teach that the

RFB4 conjugate inhibited protein synthesis when administered to mice with tumors and extended the mean survival time, and that Reiter *et al.* teach a general method of stabilizing Fv's with cysteine residues to produce a disulfide-stabilized antibody. The rejection further alleges that Kuan *et al.* teach that, in the three instances they studied, the dsFv immunotoxins were more stable. Although the rejection acknowledges that the references *do not* teach the amino acid sequence of the V_H and V_L (emphasis added), the rejection concludes that it would have been obvious that the antibody of Ghetie *et al.*, would have the variable chain sequences as set out in SEQ ID NOs:2 and 4. Applicants traverse the rejection.

In order to establish a *prima facie* case of obviousness, the rejection must demonstrate that: (1) there is some suggestion or motivation to modify the reference or combine the reference teachings; (2) there is a reasonable expectation of success: and (3) the prior art references suggest all the claim elements. *See, e.g.*, MPEP § 2143; *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991). As acknowledged by the Examiner, the cited art fails to teach all of the claim elements, namely a recombinant RFB4 antibody with the claimed sequence.

The present invention is drawn to *recombinant* immunoconjugates comprising an anti-CD22 antibody with cysteine residues at designated positions, expression vectors, antibodies, and methods of using such compositions. Applicants submit that, in order to properly evaluate the claimed invention for obviousness, the prior art teaching must also teach or suggest the sequence of the anti-CD22 antibody variable chain regions.

The constructs of Ghetie were created by chemical conjugation methods (*see, e.g.*, Shen *et al*, *Int. J. Cancer* 42:792-797, 1988 submitted herewith as Appendix B) . Ghetie *et al.* do not teach a recombinant immunotoxin, particularly an immunotoxin comprising an antibody with variable regions including cysteine residues as set forth in the claims. Moreover, at the time of the invention, the recombinant immunotoxin could not have been made in the absence of the knowledge of the nucleic acid and amino acid sequences, as proper positioning of the cysteine residues that are incorporated for the disulfide stabilization would not have been possible. The rejection has therefore failed to show that the three cited references could be combined to arrive at the claimed invention. Accordingly the rejection has failed to establish a *prima facie* case of obviousness. Applicants therefore respectfully request withdrawal of the rejection.

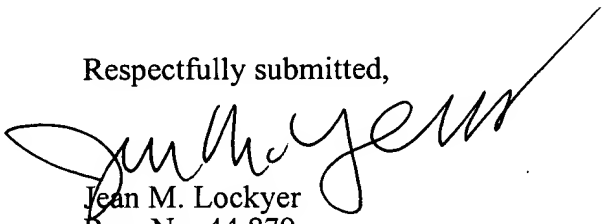
Claims 37 and 38 were rejected as allegedly unpatentable over Kreitman *et al.*, and further in view of Ghetie *et al.* This rejection is obviated in view of the cancellation of claims 37 and 38.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



Jean M. Lockyer
Reg. No. 44,879

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, 8th Floor
San Francisco, California 94111-3834
Tel: (415) 576-0200
Fax: (415) 576-0300
JML
SF 1210476 v1

APPENDIX A
ALL CURRENTLY PENDING CLAIMS

1. (amended) A recombinant immunoconjugate, comprising a therapeutic agent or a detectable label [peptide bonded] covalently linked to a recombinant [anti-CD22] antibody that binds an extracellular epitope of CD22 (an "anti-CD22 antibody") having a V_H with a cysteine at amino acid position 44 and a V_L with a cysteine at amino acid position 100.

2. (as filed) The recombinant immunoconjugate of claim 1, wherein said therapeutic agent is a toxin.

3. (as filed) The recombinant immunoconjugate of claim 2, wherein said toxin is a *Pseudomonas* exotoxin (PE) or a cytotoxic fragment thereof.

4. (as filed) The recombinant immunoconjugate of claim 3, wherein said cytotoxic fragment is PE38.

5. (amended) The recombinant immunoconjugate of claim 1, wherein said anti-CD22 antibody is [an RFB4] a binding fragment that binds a same epitope as an RFB4 disulfide-stabilized Fv (dsFv) comprising a variable heavy (V_H) chain as set out in SEQ ID NO:2, wherein a Cys residue is substituted for Arg at position 44; and a variable light (V_L) chain as set out in SEQ ID NO:4, wherein a Cys residue is substituted for Gly at position 100.

6. (amended) The recombinant immunoconjugate of claim 1, wherein said antibody comprises a variable heavy (V_H) chain [substantially similar to SEQ ID NO:2] at least 90% identical to that set out in SEQ ID NO:2 over a comparison window of 10 amino acids, and a variable light (V_L) chain [substantially similar to SEQ ID NO:4] at least 90% identical to that set out in SEQ ID NO:4 over a comparison window of 10 amino acids; and further, wherein said antibody binds to the same epitope as an RFB4 antibody comprising a V_H chain of SEQ ID NO:2 and a V_L chain of SEQ ID NO:4.

7. (amended) The recombinant immunoconjugate of claim 3, wherein said variable heavy (V_H) chain is [peptide bonded] covalently linked to the carboxyl terminus of said toxin.

8. (amended) The recombinant immunoconjugate of claim 6, wherein said V_H chain is [peptide bonded] covalently linked to said V_L chain through a linker peptide.

9. (as filed) The recombinant immunoconjugate of claim 6, wherein said V_H chain is linked to said V_L chain through a cysteine-cysteine disulfide bond.

10. (as filed) The recombinant immunoconjugate of claim 8, wherein said linker peptide has the sequence of SEQ ID NO:5.

11. (amended) An expression cassette encoding a recombinant immunoconjugate[,] comprising a sequence encoding for a toxin peptide and an [anti-CD22] antibody that binds to an extracellular epitope of CD22 (an "anti-CD22" antibody) having a V_H encoding for a cysteine at amino acid position 44 and a V_L encoding for a cysteine at amino acid position 100.

12. (amended) The expression cassette of claim 11, wherein said antibody is a binding fragment that binds to a same epitope as an RFB4 disulfide-stabilized Fv (dsFv) comprising a variable heavy (V_H) chain as set out in SEQ ID NO:2, wherein a Cys residue is substituted for Arg at position 44; and a variable light (V_L) chain as set out in SEQ ID NO:4, wherein a Cys residue is substituted for Gly at position 100.

13. (as filed) The expression cassette of claim 11, wherein said toxin is a *Pseudomonas* exotoxin (PE) or a cytotoxic fragment thereof.

14. (as filed) The expression cassette of claim 11, wherein said cytotoxic fragment is PE38.

15. (amended) The expression cassette of claim 11, wherein said antibody comprises a variable heavy (V_H) chain [substantially similar to SEQ ID NO:2] at least 90% identical to that set out in SEQ ID NO:2 over a comparison window of 10 amino acids, and a variable light (V_L) chain [substantially similar to SEQ ID NO:4] at least 90% identical to that set out in SEQ ID NO:4 over a comparison window of 10 amino acids; and further, wherein said antibody binds to the same epitope as an RFB4 dsFV as set out in claim 12.

16. (as filed) The expression cassette of claim 15, further comprising a sequence encoding for a linker peptide having the sequence of SEQ ID NO:5.

17. (as filed) A host cell comprising an expression cassette of claim 11.

18. (canceled) A V_H sequence substantially similar to that of SEQ ID NO:2.

19. (canceled) A V_L sequence substantially similar to that of SEQ ID NO:4.

20. (canceled) A nucleic acid sequence substantially similar to that of SEQ ID NO:1.

21. (canceled) A nucleic acid sequence substantially similar to that of SEQ ID NO:3.

22. (amended) A method for inhibiting the growth of a malignant B-cell that expresses a CD22 molecule on the surface of the cell, said method comprising:

contacting said malignant B-cell with an effective amount of a recombinant immunoconjugate of claim 1, thereby inhibiting the growth of the malignant B-cell.

23. (as filed) The method of claim 22, wherein said toxin is a *Pseudomonas* exotoxin (PE) or a cytotoxic fragment thereof.

24. (as filed) The method of claim 22, wherein said malignant B-cell is contacted *in vivo*.

25. (as filed) The method of claim 22, wherein said malignant B-cell is selected from the group consisting of: a rodent B-cell, a canine B-cell, and a primate B-cell.

26. (as filed) The method of claim 23, wherein said cytotoxic fragment is a PE38 fragment.

27. (amended) The method of claim 22, wherein said immunoconjugate [is an RFB4 binding fragment] comprises an antibody binding fragment that binds to a same epitope as an RFB4 disulfide-stabilized Fv (dsFv) comprising a variable heavy (V_H) chain as set out in SEQ ID

NO:2, wherein a Cys residue is substituted for Arg at position 44; and a variable light (V_L) chain as set out in SEQ ID NO:4, wherein a Cys residue is substituted for Gly at position 100.

28. (amended) The method of claim 22, wherein said immunoconjugate comprises an antibody comprising a variable heavy (V_H) chain [of SEQ ID NO:2 and a variable light (V_L) chain of SEQ ID NO:4] at least 90% identical to that set out in SEQ ID NO:2 over a comparison window of 10 amino acids, and a variable light (V_L) chain at least 90% identical to that set out in SEQ ID NO:4 over a comparison window of 10 amino acids; and further, wherein said antibody binds to the same epitope as an RFB4 antibody comprising a V_H chain of SEQ ID NO:2 and a V_L chain of SEQ ID NO:4.

29. (amended) The method of claim 23, wherein a variable heavy chain is [peptide bonded] covalently linked at the carboxyl terminus of said toxin.

30. (amended) The method of claim 29, wherein said V_H chain is [peptide bonded] covalently linked to said V_L chain through a linker peptide.

31. (as filed) The method of claim 29, wherein said V_H chain is linked to said V_L chain through a cysteine-cysteine disulfide bond.

32. (as filed) The method of claim 31, wherein said linker peptide has the sequence of SEQ ID NO:5.

33. (canceled) An anti-CD22 antibody comprising a variable heavy (V_H) chain substantially similar to SEQ ID NO:2 and a variable light (V_L) chain substantially similar to SEQ ID NO:4.

34. (canceled) The anti-CD22 Fv fragment of claim 33, wherein said antibody is detectably labeled.

35. (canceled) The antibody of claim 33, wherein said antibody is conjugated to a therapeutic agent.

36. (canceled) The antibody of claim 33, wherein said therapeutic agent is a *Pseudomonas* exotoxin (PE) or cytotoxic fragment thereof.

37. (canceled) A method for detecting the presence of CD22 protein in a biological sample, said method comprising:

(a) contacting said biological sample with an anti-CD22 antibody comprising a variable heavy (V_H) chain substantially similar to SEQ ID NO:2 and a variable light (V_L) chain substantially similar to;

(b) allowing said antibody to bind to said CD22 protein under immunologically reactive conditions, wherein detection of said bound antibody indicates the presence of said CD22 protein.

38. (canceled) The method of claim 37, wherein said antibody is detectably labeled.

39. (canceled) The method of claim 37, wherein the method is performed *in vivo* in a mammal.

40. (new) An isolated nucleic acid encoding a V_H chain comprising an amino acid sequence as set out in SEQ ID NO:2.

41. (new) An isolated nucleic acid encoding a V_L chain comprising an amino acid sequence as set out in SEQ ID NO:4.

42. (new) An isolated nucleic acid encoding a V_H chain comprising a conservatively modified variant of an amino acid sequence set forth in SEQ ID NO:2.

43. (new) An isolated nucleic acid encoding a V_L chain comprising a conservatively modified variant of an amino acid sequence set forth in SEQ ID NO:4.

44. (new) An antibody that binds to an extracellular epitope of CD22 (an "anti-CD22 antibody") comprising a variable heavy (V_H) chain that is a conservatively modified variant of SEQ ID NO:2 and a variable light (V_L) chain that is a conservatively modified variant of SEQ ID NO:4, wherein the antibody binds to the same epitope as an RFB4 antibody comprising a V_H chain of SEQ ID NO:2 and a V_L chain of SEQ ID NO:4.

45. (new) The anti-CD22 antibody of claim 44, wherein said antibody is detectably labeled.

46. (new) The antibody of claim 44, wherein said antibody is conjugated to a therapeutic agent.

47. (new) The antibody of claim 46, wherein said therapeutic agent is a *Pseudomonas* exotoxin (PE) or cytotoxic fragment thereof.

48. (new) A method for detecting the presence of CD22 protein in a biological sample, said method comprising:

(a) contacting said biological sample with an anti-CD22 antibody of claim 44;

(b) binding said antibody to said CD22 protein under immunologically reactive conditions to form an antibody-CD22 protein complex, wherein detection of said complex indicates the presence of said CD22 protein.

49. (new) The method of claim 48, wherein said antibody is detectably labeled.